SHORT REPORT

Epidemiology of recurrent genital herpes simplex virus types 1 and 2

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Objectives: To describe the epidemiology of type specific recurrent genital herpes, and to compare the duration of recurrent genital lesions caused by herpes simplex virus (HSV) types 1 and 2.

Methods: Participants were enrolled at clinics across the United States. Adults suspected of having active genital herpes were eligible. Lesions were cultured for HSV and typed. Data from 940 participants with recurrent culture positive HSV lesions were analysed. Pearson's χ^2 and Fisher's exact tests, multivariate logistic regression models, and a stratified Cox proportional hazards model were used to compare epidemiological characteristics and lesion duration of HSV-1 and HSV-2.

Results: HSV-1 was present in 4.2% of the recurrent HSV culture positive lesions. HSV-1 was most prevalent among whites (6.5%) and individuals with 0–2 recurrences in the previous year (9.1%) and, among men, in those with rectal/perirectal lesions (13.2%). Longer lesion duration was not significantly associated with virus type (hazard ratio (HR) 0.95, 95% confidence interval (CI) 0.65 to 1.38, p=0.79), but was associated with male sex (HR 0.85, 95% CI 0.74 to 0.99, p=0.04), and HIV seropositivity (HR 0.62, 95% CI 0.48 to 0.81, p<0.01).

Conclusions: The authors found that, in the United States, recurrent genital HSV-1 is relatively rare in the STD and HIV clinic setting, especially among black people. Among men, rectal/perirectal recurrent lesions are more likely to be caused by HSV-1 than are penile lesions. In addition, lesion duration depends on sex and HIV status but not virus type. These findings shed new light on the type specific epidemiology of recurrent genital HSV, and suggest that type specific testing can inform the prognosis and management of genital herpes.

Genital herpes, a disease marked by recurrent ulcerative lesions, is one of the most prevalent sexually transmitted diseases (STDs).[1 2] Herpes simplex virus type 2 (HSV-2) is the most common cause, but recent reports suggest that an increasing share of genital herpes is caused by herpes simplex virus type 1 (HSV-1).[3 4]

Although primary disease is similar for both genital HSV-1 and HSV-2,[5] primary genital HSV-1 infection is less likely than HSV-2 infection to result in recurrent disease,[6 7] and the risk of asymptomatic viral shedding is less for patients with genital HSV-1.[8] Little is known, however, about other epidemiological and clinical differences between recurrent genital HSV-1 and HSV-2.

The objective of this study was to describe the epidemiology of type specific recurrent genital herpes in a large, geographically diverse sample, and to compare the duration of recurrent genital HSV-1 and HSV-2 lesions.

METHODS

Study design

Data were collected as part of a cross sectional surveillance study to assess the prevalence of aciclovir resistance in genital herpes.[9] Participants were enrolled at 22 STD and HIV clinics in seven urban areas across the United States from October 1996 to April 1998. Eligible participants were 18 years and older and were suspected of having active genital herpes. Participants' genital lesions were cultured for HSV and positive cultures were typed.[9] Participants also answered a short questionnaire.

Analysis

We analysed data from 940 participants who reported a previous occurrence of genital herpes and whose current lesions cultured positive for HSV. We calculated proportions of HSV-1 and HSV-2 according to various epidemiological characteristics and evaluated significance of univariate associations using Pearson's χ^2 and Fisher's exact tests. We used multivariate logistic regression models to identify independent risk factors for type specific infections. The final model included variables whose associated p value in the univariate analysis was less than 0.2, and an interaction term for sex and lesion site.

We used a stratified Cox proportional hazards model to detect differences in the duration of genital lesions (number of days the preceding genital herpes episode lasted) caused by HSV-1 compared with those caused by HSV-2. The model stratified by race and controlled for sex, age, ethnicity, HIV status, type of sexual partners in the preceding year (none, opposite sex, same sex, both sexes), and whether the preceding episode was known to be a recurrence. Because we modelled time until the lesion healed, longer lesion duration corresponded to a smaller hazard.

RESULTS

Among the HSV positive cultures, 4.2% were positive for HSV-1 and 95.8% for HSV-2. The proportion of HSV-1 was significantly higher in white people and individuals with 0–2 recurrences in the previous 12 months and, among men, in those with rectal/perirectal lesions rather than penile lesions (table 1). Although the proportion of HSV-1 was also higher among women and individuals reporting same sex partners only, these differences were not statistically significant. In multivariate analyses, the significant associations persisted;

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Table 1 Univariate associations between HSV type and demographic, clinical, and behavioural variables

Variable		HSV-1		HSV-2		Odds ratio	95% CI	p Value†
		No	%	No	%			
Sex								
	Male	20	3.5	555	96.5	Referent		
	Female	19	5.3	341	94.7	1.55	(0.81 to 2.94)	0.18
Age								
	<20	1	2.9	33	97.1	Referent		
	20–29	19	5.1	352	94.9	1.78	(0.23 to 13.73)	1.0‡
	30–39	9	2.9	296	97.1	1.00	(0.12 to 8.17)	1.0‡
	40–49	8	4.8	158	95.2	1.67	(0.20 to 13.82)	1.0‡
	50–59	2	3.8	50	96.2	1.32	(0.12 to 15.15)	1.0‡
	60+	0	0	12	100	ND	ND	1.0‡
Race								
	White	29	6.5	418	93.5	Referent		
	Black	5	1.3	390	98.7	0.18	(0.07 to 0.48)	<0.01
	Other	5	5.3	90	94.7	0.80	(0.30 to 2.13)	0.65
Ethnicity								
	Non-Hispanic	34	4.2	785	95.9	Referent		
	Hispanic	4	4.2	92	95.8	1.00	(0.35 to 2.89)	1.0‡
Duration of previous lesion								
	0–5 days	14	3.7	369	96.3	Referent		
	6–7 days	11	4.0	265	96.0	1.09	(0.49 to 2.45)	0.83
	8–10 days	5	4.5	107	95.5	1.23	(0.43 to 3.50)	0.70
	11+ days	9	5.3	160	94.7	1.48	(0.63 to 3.50)	0.37
Episodes in previous 12 months								
	0–2	19	9.1	191	90.9	Referent		
	3–4	17	3.4	484	96.6	0.35	(0.18 to 0.69)	<0.01
	5+	3	1.3	226	98.7	0.13	(0.04 to 0.46)	<0.01
Years since 1st genital herpes lesion								
	1 or less	17	4.3	382	95.7	Referent		
	2–5	15	5.5	258	94.5	1.31	(0.64 to 2.66)	0.46
	6+	7	2.6	261	97.4	0.60	(0.25 to 1.47)	0.26
Ever used anti-herpes drugs								
	No	20	3.9	499	96.2	Referent		
	Yes	18	4.4	387	95.6	1.16	(0.61 to 2.22)	0.65
Aciclovir resistant isolate								
	No	39	4.2	886	95.8	Referent		
	Yes	0	0	15	100	ND	ND	1.0‡
HIV status								
	Negative	31	4.0	746	96.0	Referent		
	Positive	8	5.0	152	95.0	1.27	(0.57 to 2.81)	0.56
Sex partners in previous 12 months								
	None	4	3.9	99	96.1	Referent		
	Opposite sex only	28	3.8	716	96.2	0.97	(0.33 to 2.82)	1.0‡
	Same sex only	7	9.9	64	90.1	2.71	(0.76 to 9.62)	0.12‡
	Both	0	0	22	100	ND	ND	1.0‡
Lesion site								
	Women only							
	Vulva	11	6.4	160	93.6	Referent		
	Cervico-vaginal	3	5.8	49	94.2	0.89	(0.24 to 3.32)	1.0‡
	Rectal/perirectal	3	7.3	38	92.7	1.15	(0.31 to 4.32)	0.74‡
	Thigh	1	1.2	61	98.4	0.24	(0.03 to 1.89)	0.19‡
	Other	0	0	14	100	ND	ND	1.0‡
	Multiple sites	1	7.1	13	92.9	1.12	(0.13 to 9.36)	1.0‡
	Men only							
	Penis	11	2.5	434	97.5	Referent		
	Rectal/perirectal	9	13.2	59	86.8	6.02	(2.39 to 3.32)	<0.01‡
	Thigh	0	0	37	100	ND	ND	1.0‡
	Other	0	0	19	100	ND	ND	1.0‡
	Multiple sites	0	0	3	100	ND	ND	1.0‡

†Pearson's χ^2 p value, except where otherwise indicated. ‡Fisher's exact test, two tailed p value. ND, not determined because of zero cells.

in addition, among those without rectal/perirectal lesions, the proportion of HSV-1 was significantly higher in women than in men (table 2).

There was little difference between the distributions of lesion duration for HSV-1 and HSV-2 (table 1). In a stratified Cox proportional hazards model, longer lesion duration was not significantly associated with virus type (HSV-1 compared with HSV-2: HR 0.95, 95% CI 0.65 to 1.38, p = 0.79), but was associated with male sex (HR 0.85, 95% CI 0.74 to 0.99, p = 0.04), and HIV seropositivity (HR 0.62, 95% CI 0.48 to 0.81, p<0.01).

DISCUSSION

In one of the largest studies to date of recurrent genital herpes, we examined the epidemiology of type specific HSV infection. Several aspects of the study were unique. We enrolled patients from many US geographical areas, included HIV infected patients, had sufficient patients to study recurrent genital HSV-1, and used statistical techniques that allowed for the identification of independent risk factors for type specific culture positivity and lesion duration. In this population, HSV-1 caused 4.2% of recurrent lesions. HSV-1 was more likely to be present in recurrent lesions of white

Table 2 Multivariate associations between HSV-1 and selected variables

Variable		Odds ratios	95% CI	p Value
Men				
	No rectal lesions	Referent		
	Rectal lesions	8.41	(2.38 to 29.73)	<0.01
Women				
	No rectal lesions	Referent		
	Rectal lesions	1.08	(0.28 to 4.09)	0.92
Persons without rectal lesions				
	Men	Referent		
	Women	2.41	(1.07 to 5.39)	0.03
People with rectal lesions				
	Men	Referent		
	Women	0.31	(0.06 to 1.68)	0.09
Race				
	White	Referent		
	Black	0.16	(0.06 to 0.42)	<0.01
	Other	0.77	(0.28 to 2.14)	0.61
Sex partners in previous 12 months				
	None	Referent		
	Opposite sex only	2.35	(0.62 to 8.97)	0.21
	Same sex only	2.02	(0.51 to 8.00)	0.31
	Both	ND		
Number of episodes in previous 12 months				
	0–2	Referent		
	3–4	0.33	(0.16 to 0.67)	<0.01
	5+	0.09	(0.03 to 0.33)	0.02

Odds ratios (OR) compare the odds of HSV-1 infection by variable category, so OR >1 means that HSV-1 is more common in a given category than in the referent category. ND, not determined because of insufficient numbers.

people, individuals with few recurrences during the past year and, among men, in rectal/perirectal lesions rather than penile lesions. Lesion duration did not vary by HSV type, but did vary by sex and HIV status.

The percentage of recurrent lesions caused by HSV-1 (4.2%) was considerably less than the percentage of first episode lesions caused by HSV-1 (14.6%) in other participants at the same clinical sites (Jevitt *et al*, in preparation); this is consistent with reports that genital HSV-1 recurs less frequently than genital HSV-2.[6 7 10] This conclusion is also supported by the higher prevalence of HSV-1 among individuals with fewer recurrences during the past year (table 2). The proportion of recurrent lesions caused by HSV-1 (4.2%) was less than half that reported by Lafferty *et al* (9.9%).[10] This difference does not appear to be explained by differences in sex practices, as our HSV-1 percentages were less within the subgroups of heterosexual men, heterosexual women, and men who have sex with men (MSM). The differences might be due to overall differences in the patient populations, because our study was from numerous clinical sites of wide geographical distribution within the United States whereas Lafferty *et al*[10] enrolled patients at one STD clinic in Seattle.

The ratio of HSV-1 prevalence in black compared to white people was similar for recurrent (1.3% *v* 6.5%, odds ratio (OR) = 0.18) and first episode lesions (5% *v* 27%, OR = 0.1) (Jevitt *et al*, in preparation), suggesting that genital HSV-1 recurrence rates do not differ by race, but that white people are simply more likely to be genitally infected with HSV-1. This difference may be due to white people having a higher frequency of receptive oral sex[11] or being less likely to have acquired oral HSV-1 at an early age.[12]

Recurrent rectal/perirectal lesions in men were significantly more likely to be caused by HSV-1 than were recurrent penile lesions (OR = 8.4). This was also true for first episode lesions but differences by anatomical site were less marked (OR = 2.6) (Jevitt *et al*, in preparation), suggesting that HSV-1 is both more likely to infect the rectal/perirectal region and more likely to recur in individuals whose primary lesions were in this region. Among MSM, the higher prevalence of HSV-1 in rectal/perirectal lesions might be explained by oral/anal transmission of HSV-1, either by oral–anal contact or by use of saliva as a lubricant for anal sex.

Finally, recurrent lesion duration did not differ by viral type: a finding recently reported by Engelberg *et al*.[7] Our study adds the observation that the lack of difference is not due to confounding by variables such as sex, race, sexual orientation, or lesion site. Our results are consistent with the previously established association between longer lesion duration in men[13] and HIV infected individuals.[2]

In summary, we found that in the United States, recurrent genital HSV-1 is relatively rare in the general STD and HIV clinic setting, especially among black people. Among men, rectal/perirectal recurrent lesions are more likely to be caused by HSV-1 than are penile lesions. In addition, lesion duration depends on sex and HIV status but not virus type. These findings shed new light on the type specific epidemiology of recurrent genital HSV, and suggest that type specific testing can inform the prognosis and management of genital herpes.

DISCLAIMER

The use of trade names and commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

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CONTRIBUTORS

LS was responsible for the analysis and interpretation of the data and drafting of the manuscript; MC supervised the analysis and interpretation and provided critical revision of the manuscript for important intellectual content; MR was the principal investigator for this study and assisted in revision of the manuscript; JG was an investigator for this study and assisted in revision of the manuscript; NW directed the laboratory component of this study and assisted in revision of the manuscript; WR supervised this investigation and assisted in revision of the manuscript.

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